Remarks/Arguments

Claims 1, 4-8, 10-11, 13-15, 32 and 35-40 are pending in the application. All claims have been rejected. Claims 36, 38 and 40 are revised to delete the phrase "preferred by Cdk5 kinase activity" to better clarify the claims. Support for deletion of this term and the clear meaning of a "candidate sequence" can be found on page 5 lines 1-3 of the specification. Claim 37 was revised to delete "reference to amino acid positions of" to better clarify Applicants meaning. Reconsideration and withdrawal of the rejections are respectfully requested in light of the following remarks.

Inclusion of SEQ ID Nos: 4 and 5 is not new matter

Examiner's Arguments

The Examiner maintained the objection to the amendments that incorporate SEQ ID Nos: 4 and 5 into the specification under 35 U.S.C. 132(a) for introducing new matter into the disclosure. The Examiner asserts that according to MPEP § 608.01(p) incorporation by reference of material in a non-patent document "must be set forth in the specification and must: (1) Express a clear intent to incorporate by reference by using the root words "incorporat(e)" and "reference" (e.g., "incorporate by reference"); and (2) Clearly identify the referenced patent, application, or publication." See 37 § 1.57(b). Furthermore the Examiner states that MPEP § 608.01(p) further states, "[i]f a reference to a document does not clearly indicate an intended incorporation by reference, examination will proceed as if no incorporation by reference statement has been made and the Office will not expend resources trying to determine if an incorporation by reference was intended." The Examiner states that he can find no provision that excludes applications having a filing date of the instant application from being subject to 37 CFR 1.57 and MPEP 608.01(p) and applicant has presented no evidence of such. The Examiner asserts that while the GenBank Accession Numbers are cited in the specification, this appears to be "mere reference to material," which, according to 37 CFR 1.57(g)(1), "does not convey an intent to incorporate the material by reference."

The Examiner maintained the rejection of claims 1, 4-8, 10-11, 13-15, 32 and 35 under U.S.C. 112, first paragraph as failing to comply with the written description requirement for introducing new matter. For the reasons stated above, the Examiner

asserts that the claim(s) referring to SEQ ID Nos: 4 and 5 contain new matter which was not described in the specification.

Applicants' Arguments

Applicants respectfully disagree with the preceding objection and rejection of the claims. Applicants argue that inclusion of the genbank references in the *definition* of Dab1 is more than a mere reference to material. Furthermore, the Examiner agreed with this position when, prior to making the present objection and rejection, the Examiner previously determined that SEQ ID NOs:4 and 5 were intended to be incorporated by reference based on the inclusion of the appropriate genbank numbers and proceeded to expend resources to examine the application.

The Examiner withdrew an objection in the 8/22/05 Office Action, stating that the disclosed GenBank Accession Number in the specification is considered to be an inherent "incorporation by reference", and proceeded to examine the claims based on the inclusion of SEQ ID NO:4 (mouse Dab1). In the Office Action dated 2/21/06, the Examiner allowed a claim that incorporated SEQ ID NO:4 and indicated that 2 other claims, one that incorporated SEQ ID NO:4 and another that incorporated SEQ ID NO:5, would be allowed if written in independent form.

However, in the Office Action dated 5/1/06, the Examiner reconsidered this determination and rejected the claims citing 37 C.F.R.§1.57 and MPEP § 608.01(p). The Examiner asserts that the originally filed disclosure does not provide support for SEQ ID NO:4 and SEQ ID NO:5 based on the fact that the root words "incorporate" and "reference" do not appear in the specification.

The regulation cited to support this rejection, 37 C.F.R.§1.57, was added on Sept. 21, 2004 and became effective Oct. 21, 2004, well after the February 19, 2002 filing date of the present application. Furthermore, MPEP § 608.01(p) was not amended until Oct. 21, 2004 to include the language stated in the above objection by the Examiner. Applicants maintain that a patent application should not be faulted for failing to adhere to rules established well after its filing date. In support of Applicants' arguments, the Federal Register Vol. 69, No. 182: 56506 (Sept. 21, 2004) when discussing 37 C.F.R. §1.57 states "Where there was clear specific intent to attempt to incorporate an identifiable document for which a correction was not new matter before the rule change

will not be new matter after the rule change." In addition, the burden does not fall on Applicants to prove that this regulation should not retroactively apply to their application as the Examiner suggests. Rather, the burden falls on the Examiner to prove that it is fair and reasonable to apply this regulation to applications filed before they were promulgated.

Even if Applicants are held to this standard, 37 C.F.R. § 1.57 (g)(1) allows correction to comply with paragraph (b)(1) of this section if the application as filed clearly conveys an intent to incorporate the material by reference. 37 C.F.R. § 1.57 (g)(2) states that [a] correction to comply with paragraph (b)(2) of this section is permitted for material that was sufficiently described to uniquely identify the document.

On page 4, lines 24-25 of the specification, Applicants specifically define Dab1 proteins as including proteins cloned from genbank accession numbers 3288851 and 1771281. As Applicants have argued earlier, including these genbank numbers as part of the definition of Dab1 reflects Applicants' intent for these publications to be incorporated by reference. Applicants also indicated during prosecution that the sequences incorporated into the specification were the sequences found in the genbank accession numbers at the time of filing of the application. Thus, Applicants have fulfilled the requirements of 37 § 1.57(g)(1) and (g)(2).

In light of the arguments presented above, Applications have overcome the objection to the specification and rejection of claims 1, 4-8, 10-11, 13-15, 32 and 35 under U.S.C. 112, first paragraph. Reconsideration and withdrawal of such are respectfully requested.

The term "candidate sequence" is definite

Examiner's Arguments

The Examiner rejected claims 36-40 for use of the term "candidate sequence preferred by cdk5 activity" under 35 U.S.C. 112, second paragraph as being indefinite. The Examiner acknowledged the definition of the term "candidate sequence" at page 5 of the specification as being a sequence of amino acids which contains a serine followed by a proline in +1 position and a lysine in +3 position, the serine being a preferred site for Cdk5 activity. However, the Examiner asserts that this definition is unclear from the specification and the claims as to which of those sequences encompassed by the definition are intended as being "preferred" over those that are not "preferred" by a

"Cdk5" polypeptide, which is defined in the specification as encompassing any protein "with serine/threonine kinase activity that is structurally homologous to the mitotic cyclin dependent kinases."

Applicants' Arguments

Applicants have argued and maintain that the specification specifically defines a "candidate sequence" as a sequence of amino acids which contains a serine followed by a proline in the +1 position and a lysine in the +3 position, the serine being a preferred site for Cdk5 activity (Songyanget al., Mol Cell Biol, 16:6486-6493, 1996). Songyang et al. teach that his sequence is a distinct optimal peptide substrate for the Cdk5 kinase. Since the term "candidate sequence" is clearly defined in the specification, Applicants have removed the term "preferred by cdk5 kinase activity" from the claims to avoid confusion.

Applicants respectfully request reconsideration and withdrawal of the rejection of claims 36-40 under 35 USC § 112, second paragraph in view of the amendment to the claims and remarks above.

Use of recitation of "GenBank accession number" is definite

Examiner's Arguments

The Examiner rejected claim 39 as being indefinite by reference to "GenBank accession number 1771281." The Examiner asserts that since a sequence of a GenBank Accession is variable, it is unclear as to whether the polypeptide encoded by GenBank accession number 1771281 is limited to the polypeptide encoded by the nucleotide sequence of GenBank accession number 1771281 at the time of the invention, or whether the term is intended as encompassing future revised sequences. The Examiner asserts Applicants' prior argument that "any changes that might be made to the Cdk5 or Dab1 sequence would not be expected to change the characteristics of these proteins" would appear that Applicant's intend for the claim to encompass any polypeptides encoded by future revised sequences. The Examiner also asserts that GenBank accession number 1771281 indicates that the encoded polypeptide is mDab555 not a Dab1 protein as recited in the claims.

Applicants' Arguments

Applicants respectfully disagree with the conclusion of the Examiner. Applicants intend that the nucleotide sequence of Genbank accession numbers be limited to the

sequence listed at the time of the invention. In the revision history for accession numbers, each date the accession number was revised is clearly shown. Furthermore, a link is provided so that one can review the contents of the accession number for each date prior to a revision. Since a person of skill in the art knows the filing date of the present application, that person can easily access the sequence in genbank that was known at that time. Therefore, the use of genbank accession numbers in the claims is clear and definite.

As for the Examiner's assertion that the claims are indefinite because the Genbank accession number describes the protein as mDab555 instead of Dab1, Applicants point to the definition provided in the specification specifically stating that Dab1 proteins include those cloned from genbank numbers 3288851 and 1771281.

Applicants did not intend for claim 39 to encompass any polypeptides encoded by future revised sequences and respectfully request reconsideration and withdrawal of the rejection of claim 39 made under 35 USC § 112, second paragraph.

Use of the term "alignment of Dab1 with SEQ ID Nos: 1 or 2" is definite

Examiner's Arguments

The Examiner rejected claim 37 as being indefinite in the recitation of "reference to amino acid positions of SEQ ID NO:1" and "reference to amino acid positions of SEQ ID NO:2." The Examiner asserts that it is unclear as to what position of SEQ IDNO:1 and/or 2 that are intended as being encompassed by the claims and suggests that Applicants clarify the meaning of the noted phrase.

Applicants' Arguments

Applicants' intent is to identify a serine in Dab1 that corresponds to position 3 of SEQ ID NO:1 or position 21 of SQ ID NO:2 when Dab1 is aligned with either SEQ ID NO:1 or SEQ ID NO:2. Applicants has revised claim 37 to remove "reference to amino acid positions of". Applicants respectfully submit that the rejection made under 35 USC § 112, second paragraph should not be applied to revised claim 37 and request withdrawal of the rejection.

Use of SEQ ID NO:3 as a limitation for Dab1 proteins is not new matter

Examiner's Arguments

The Examiner rejected claim 40 that incorporated SEQ ID NO:3 as a structural limitation for Dab1 proteins under 35 U.S.C. 112, first paragraph for inserting new matter.

The Examiner maintains that while all members of the genus of Dab1 polypeptides comprise the structural feature of the 14 amino acid peptide of SEQ ID NO:3, this structural feature does not constitute a "substantial portion" of the genus of recited Dab1 polypeptides. Thus, the Examiner maintains that the specification failed to adequately describe the claimed invention. The Examiner acknowledged that SEQ ID NO:3 may be present in other naturally occurring Dab1 proteins and that the claim requires all members of the genus to have this common structural feature, but questions whether or not the specification provides descriptive support for the limitation of "Disabled 1 (Dab1) protein comprising SEQ ID NO:3." The Examiner asserted that SEQ ID NO:3, while being disclosed in the specification as a peptide used as an antigen in the production of a phosphoantibody, does not appear to provide descriptive support for a subgenus of Dab1 polypeptides.

Applicants' Arguments

As Applicants have shown and the Examiner acknowledges, SEQ ID NO:3 comprises 14 amino acids found in the c-terminal portion of the Dab1 protein in several different species including mice, rats, humans, birds, dogs and cows. Proteins other than Dab1, even closely related proteins such as Dab2, do not share this sequence. In response to the Examiner's prior rejection of claims stating that a genus requires a precise definition, such as structure, formula or chemical name of the claimed subject matter to sufficiently distinguish it from other materials, SEQ ID NO:3 was provided as a common structural reference for the genus of Dab1 proteins to further supplement the other distinguishing features of Dab1 noted in the specification. A peptide having the sequence of SEQ ID NO:3, as shown in the specification, was used as an antigen to generate an antibody that binds to Dab1. The use of this peptide as an antigen reveals to one of skill in the art that this is a sequence that is characteristic of Dab 1 and useful for distinguishing Dab1 from other proteins. Furthermore, page 15 lines 16-17 state that SEQ ID NO:3 contains one of the candidate sequences (491) claimed in the instant application. Therefore, inclusion of SEQ ID NO:3 in the claims as a feature of Dab 1 is fully supported by the specification and is not new matter.

Applicants respectfully submit that the rejection of claim 40 made under 35 U.S.C. § 112, first paragraph, for inserting new matter, should be withdrawn.

The scope of Dab1 proteins is defined and disclosed

Examiner's Arguments

The Examiner rejected claims 36-38 and 40 under 35 U.S.C. § 112, first paragraph for failure to comply with the written description requirement. The Examiner asserts that claims 36-38 encompass the use of any polypeptide, including mutants and variants, having any sequence of amino acids that is considered to be an "intracellular adapter protein" and that is phosphorylated by Cdk5 activity and by reelin tyrosine kinase activity. The Examiner also asserts that there is no requirement that the genus of Dab1 proteins even have a serine residue, that claim 37 does not limit the structures of the genus of Dab1, only what is being detected by the claimed method and that outside of SEQ ID NO:3, the structures of the genus of Dab1 polypeptides in claim 40 are completely undefined.

The Examiner states that other than the two representative species of Dab1 polypeptides (GenBank accession numbers 3288851 and 1771281) the specification fails to describe any additional representative species of the recited genus of Dab1 polypeptides. The Examiner further asserts that the specification fails to disclose or provide guidance regarding those amino acids of any Dab1 polypeptide that can be altered and still maintain the ability to be phosphorylated by Cdk5 serine kinase activity and without a correlation between structure and function, the claims do little more than define the claimed invention by function, which is not sufficient to satisfy the written description requirement.

Applicant's Arguments

The invention is based on the discovery that Dab1 is specifically phosphorylated by Cdk5. Cdk5 activity is tightly controlled by its regulator, p35, making Cdk5 activity difficult to determine based on levels of Cdk5 present. Furthermore, a substrate which is selectively phosphorylated by Cdk5 had not heretofore been identified. Applicants do not rely upon the primary structure; i.e. the amino acid sequence, of any Dab1 to impart patentability upon the claimed compositions. Instead, Applicants properly rely on the knowledge of this structure to supplement the description of the novel and unobvious aspects of the invention in the specification.

Rather than creating their own definition of Dab1 as the Examiner suggests, Applicants relied upon the well known meaning of this term in the art and simply reiterated those features of Dab1 in the specification that are critical to its function in the claimed method. The specification does define Dab1 as an intracellular adapter protein that is phosphorylated by Cdk5 activity and reelin tyrosine kinase activity, which is consistent with the well known meaning in the art. In addition to the definition, the specification includes numerous scientific publications (see page14 lines 7 – 14 and page 25 lines 20 – page 26 line 12) which distinguish it from other closely related Dab proteins. Furthermore, Dr. Thomas Curran, a co-inventor of the present application and a person of skill in the art, provided an expert declaration stating that "Cdk5", "Dab1" and "Cdk5 serine kinase activity" were well known terms in the art at the time the application was filed. Because the term Dab1 was well known in the prior art, an exhaustive description does not need to be reproduced in the specification and in fact is preferably omitted according to *Hybridtech, Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986.)

In *Falkner v. Inglis*, 448 F.3d 1357, 2006 WL 1453040, Slip No. 05-1324 (Fed. Cir. May 26, 2006) the Court of Appeals for the Federal Circuit (CAFC) agreed with the Board of Patent Appeals and Interferences (BPAI) that the poxvirus-based vaccines described in the Inglis applications were adequately described and enabled even though the specification contained no poxvirus sequences or specific examples for making a poxvirus vaccine. Likewise, in *Capon et al. v. Eshar et al.,* Nos. 03-14480, 1481 (Fed. Cir. August 12, 2005), the CAFC reversed the BPAI and found that claims to chimeric genes composed of pieces of known genes did not need to recite the known gene sequences to satisfy the written description requirement.

In clarifying the written description standard in *Falkner*, the CAFC held that for purposes of the written description requirement, there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure. An underlying rationale for this holding is that the specification is written for a person of skill in the art, and it is thus unnecessary to spell out every detail when one of skill in the art would readily be convinced that the applicant possessed the invention. The court also reasoned that when accessible literature sources

clearly provide the structure of a biological macromolecule, a re-description of what is already known is not necessary. The CAFC noted that omission of such redundant information from the specification is preferred, reiterating the familiar adage that "[a] patent need not teach, and preferably omits, what is well known in the art." citing *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1534 (Fed. Cir. 1987).

In regard to the Examiner's assertion that the genus of Dab1 proteins are not required to have a serine residue, Applicants assert that the claims, as written, do require such. One cannot determine phosphorylation on a serine within a candidate sequence if Dab1 does not contain such a serine. Furthermore, the Examiner asserts that Applicants provide no guidance regarding which amino acids can be altered with Dab1 still maintaining the ability to be phosphorylated by Cdk5. On page 19 lines 26 – page 20 line 7 of the specification, Applicants show that the PTB domain of Dab1 which contains residues 1-179 and the middle region, which contains residues 180-399, were not phosphorylated in *in vitro* Cdk5 kinase assays. However, the carboxy terminal region containing residues 400-555 was phosphorylated. Furthermore, on page 21 lines 15 - 20 of the specification, Applicants describe mutants of Dab1 that have serines 491 and/or 515 replaced by alanine residues.

The term Dab 1 was well known in the art at the time the present application was filed and a person of skill in the art, with guidance from the specification, would recognize that Applicants do provide a full, clear and concise description. Therefore, Applicants respectfully submit that the rejection made under 35 USC § 112, first paragraph is improper and should not be applied to claims 36 – 38 and 40.

Claims 1, 4-8, 10-11, 13-15, 32 and 35-40 are rejected under 35 U.S.C. 112, first paragraph based on the assertion that the specification fails to reasonably provide enablement of the broad scope of the claimed methods. The Examiner's analysis of the factors set forth in In re Wands (858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) to support this rejection is summarized below along with Applicants analysis of these same factors that lead to the opposite conclusion.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art

Examiner's Arguments

The Examiner asserts that although Applicants' have stated that Dab1 is specifically phosphorylated by Cdk5, post-filing evidence suggests that Dab1 is not specifically phosphorylated by Cdk5 and refers to Ohshima et al. (Brain Res. 1140:84095, 2007). This reference teaches that Cdc2 is at least one other kinase that phosphorylates Dab1 on serine/threonine residues. The Examiner also assets that according to the reference of Takeo (Int. J. Dev. Biol. 38:185-191, 1994), cdc2 is a mitotic serine/threonine kinase and would appear to be encompassed by the specification's definition of "Cdk5" as "a protein with serine/threonine kinase activity that is structurally homologous to the mitotic cyclin dependent kinases." The Examiner also asserts that according to Patrick et al. (J. Biol. Chem. 273:24057-24064, 1998), the substrate specificity of the p35/Cdk5 kinase is similar to that of the Cdc2 and Cdk2 kinases, phosphorylating the K(S/T)PX(K/R) consensus sequence motif.

The Examiner further asserts a skilled artisan would recognize the high level of unpredictability in altering the Dab1 sequence with an expectation that the resulting polypeptide would maintain a conformation that is able to maintain specific phosphorylation on a serine by a Cdk5 polypeptide.

Applicants' Arguments

Applicants argue that the claims cite a method for detecting Cdk5 *serine kinase activity*. It was well known at the time of filing and taught in the specification that Cdk5 kinase activity is dependent upon Cdk5 being in a complex with its neuronal regulators p35 or p39 (see page 7 lines 16-20, page 14 lines 18-21 and page 19 lines 20-25 of the specification). This is a distinction between Cdk5 and Cdc2 kinase activity that a person skilled in the art would readily recognize. Therefore, Cdk5 kinase activity, as taught in the specification, is distinct from cdc2 kinase activity.

Although Ohshima teaches that Cdc2 is a kinase that phosphorylates Dab1 *in vitro*, there is no evidence that it does so within the c-terminal region on a candidate sequence as encompassed by the claims. Ohshima teaches that based on cdc2 *in vitro* phosphorylation, Dab1 is probably phosphorylated by Cdc2 kinase in Cdk5-/- embryonic brain (Figure 1 legend) and suggests that this phosphorylation may occur in the N-terminal region. On page 92, first column, second paragraph, Ohshima states: "Because Cdk5 specifically phosphorylates Ser/Thr sites in C-terminal region of p80 Dab1 and the

Ser246 of p45 Dab1, other serine/threonine kinases(s) may be involved in the phosphorylation of the N-terminal region of Dab1."

Furthermore, Ohshima teaches that Cdk5 does in fact phosphorylate Dab1 on serines 491 and 515 (page 86, first column). While Cdk5 phosphorylates other sites in the c-terminal domain of Dab1, serines 491 and 515 are the only serines within a candidate sequence in Dab1 as encompassed by the claims. Ohshima does not teach that Cdc2 or any other kinase phosphorylates these two amino acids. Claims 1, 37 and 39 are specific to serine 491 or 515, Claims 32 and 35 are specific to serine 491, and Claims 36, 38 and 40 are specific to candidate sequences in the carboxy terminal domain. Thus, Ohshima does teach that Dab1 is selectively phosphorylated by Cdk5 as claimed.

As such, a skilled artisan would recognize that a Dab1 polypeptide phosphorylated on a serine residue, as a serine is encompassed by the claims, is indicative of the Cdk5 serine kinase activity.

The amount of direction provided by the inventor and The existence of working examples

Examiner's Arguments

The Examiner asserts that the specification discloses a single working example of the claimed method. Other than this single working example, the specification fails to provide guidance as to whether other Dab1 polypeptides, including mutants and variants will have the ability to be specifically phosphorylated – and the serines that are specifically phosphorylated – by any polypeptide that is considered to be a Cdk5 as encompassed by the specification's definition. The specification fails to provide guidance for using all methods that detect activity of any "Cdk5 serine kinase activity," including *e.g.*, Cdc2 activity, as broadly encompassed by the claims.

Applicant's Arguments

On page 19 lines 26 – page 20 line 7 of the specification, Applicants show that the PTB domain of Dab1 which contains residues 1-179 and the middle region, which contains residues 180-399, were not phosphorylated in *in vitro* Cdk5 kinase assays. However, the carboxy terminal region containing residues 400-555 was phosphorylated to almost the same extent as full length Dab1. Furthermore, on page 21 lines 15 - 20 of the specification, Applicants show that a mutant of Dab1 that has serine 491 replaced by

alanine is not phosphorylated at the 491 site. Also, an alanine substitution for the 515 serine had no effect on serine 491 phosphorylation. Therefore, Applicants do teach mutations and variants that are both phosphorylated and not phosphorylated by Cdk5 serine kinase activity. Applicants have shown that a person of skill in the art can readily determine which Dab1 proteins, as encompassed by the claims, are useful for detecting Cdk5 serine kinase activity.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Examiner's Arguments

The Examiner asserts that it was not routine in the art to screen for all Dab1 polypeptides as encompassed by the claims, having a substantial number of modifications for those that have the desired activity/utility. Further, it was not routine to determine which of those "proteins with serine/threonine kinase activity that are structurally homologous to the mitotic cyclin dependent kinases" polypeptide and determine a use – if any – for such method.

In regard to Applicants' prior remarks, the Examiner does not dispute Applicants' evidence showing Cdk5 phosphorylation of serine 491 of mouse Dab1 and a sequence alignment of Dab1 from mouse, rat, and human and the structural relation between Dab1 from mouse, rat, human, dog, bird, cow, or zebrafish. However, the Examiner notes that the claims are not limited to those Cdk5 or Dab1 polypeptides that are naturally occurring. As such, Applicants' evidence is insufficient to establish an enabling disclosure for the full scope of the claimed invention.

Applicant's Arguments

As stated above, Applicants show three different fragments of Dab1. It is shown that the PTB domain of Dab1 which contains residues 1-179 and the middle region, which contains residues 180-399, were not phosphorylated in *in vitro* Cdk5 kinase assays. More importantly, Applicants show that the carboxy terminal region containing residues 400-555 was phosphorylated to almost the same extent as full length Dab1. Furthermore, on page 21 lines 15 - 20 of the specification, Applicants show that a mutant of Dab1 that has serine 491 replaced by alanine is not phosphorylated at the 491 site. Also, an alanine substitution for the 515 serine had no effect on serine 491 phosphorylation.

Methods for detection of Dab1 phosphorylation on a serine are well know in the art as are methods for substituting amino acids in a protein. Thus, it was well know in the art how to make and screen for multiple modifications in Dab1 that allow Cdk5 serine phosphorylation.

In light of the prior arguments, Applicants respectfully request withdrawal of the 35 U.S.C. 112, first paragraph rejection.

The claims are not anticipated or made obvious by the prior art

Examiner's Arguments

Claims 1, 6-8, 15, 36-37 and 39-40 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Homayouni et al. (J. Neurosci. 19:7507-7515, 1999) as evidenced by Patrick et al. (J. Biol. Chem. 273:24057-24064, 1998). The Examiner asserts that although Homayouni et al. is silent as to the presence of enzymatically active Cdk5 in COS7 cells, the evidentiary reference of Patrick et al. discloses that COS7 cells exhibit endogenous catalytically active Cdk5 and because enzymatically active Cdk5 is endogenously expressed in COS7 cells, the endogenous Cdk5 would have phosphorylated the recombinantly expressed Dab1 of Homayouni et al. While Homayouni et al. does not specifically teach detection of mouse Dab1 phosphorylation at serine 491 or 515, because Cdk5 is endogenously expressed in COS7 cells, the mouse Dab1 expressed in COS7 cells according to the method of Homayouni et al. would necessarily result in phosphorylation at serine 491 or 515, and thus at least one of the phosphoserines detected by the method of Hamayouni et al. would have necessarily included phosphoserine at position 491 or 515 of mouse Dab1. The Examiner asserts that "While applicant may argue the reference of Homayouni et al. does not recognize Dab1 as being a substrate for phosphorylation by Cdk5, it is noted that according to MPEP 2112.I, the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1454, 195 USPQ 420, 433 (CCPA 1977)."

Applicants' Arguments

In order for a prior art reference to anticipate a claim, a prior art reference must teach each and every aspect of the invention as claimed and provide guidance to enable a person of skill in the art to use the invention. Homayouni et al. does not disclose Cdk5

activity in COS7 cells nor does Homayouni suggest that Dab1 is a substrate for Cdk5 activity. Homayouni teaches that APLP1, APLP2 and APP increase serine phosphorylation of Dab1 in COS cells (figure 5, page 7511). As discussed below, contrary to the Examiner's assertion, enzymatically active Cdk5 is not endogenously expressed in COS7 cells. Although Homayouni teaches that serines in Dab1 are phosphorylated it does not teach which serines are phosphorylated, how to determine which serine is phosphorylated, or the association between serine phosphorylation and Cdk5 activity. Therefore, Homayouni fails to teach each and every element of the claimed method.

As for the 35 U.S.C. 103(a) rejection, this rejection depends on the Examiner's incorrect assertion that Patrick et al discloses that COS7 cells exhibit endogenous catalytically active Cdk5. On page 24061, second column, Patrick et al states that Cdk5, not Cdk5 activity, is endogenously present in COS7 cells. The presence of Cdk5 in these cells is not surprising, but the presence of Cdk5 activity in these cells does not follow. On page 14 lines 18 – 21 of the specification, Applicants teach that Cdk5 is ubiquitously expressed, but its catalytic activity is dependent on the neuronal regulators p35 or p39. COS7 cells would not be expected to express either of the neuronal regulators (bottom of page 1036 through page 1038 first paragraph of Tsai et al. Development 119,1029 – 1040 (1993) and Lew et al. Nature 371:423-426 (1994)). In the absence of these regulators, COS7 cells would not be expected to have Cdk5 activity. Thus, Applicants and other prior art references teach away from the fact that Cdk5 kinase activity is present in COS7 cells. Therefore, the references cited by the Examiner do not render the claims obvious.

Applicants have shown that Homayouni et al does not anticipate the present invention, nor does Homayouni et al. as evidenced by Patrick et al. render the present invention obvious. Therefore, Applicants respectfully request withdrawal of the rejections.

The Homayouni et al prior art reference cited by the Examiner was disclosed to the patent office in Applicants' information disclosure well before the first Office Action issued on 9/16/2004 and has been before the Examiner since prosecution began. Furthermore, Patrick et al. is a scientific publication from 1998. Applicants are surprised

and disappointed that the Examiner has made new rejections based on these references at this late stage of prosecution.

Conclusion

It is believed that the objection to the specification and rejections of Claims 1, 4-8, 10-11, 13-15, 32 and 35-40 have been overcome and request allowance of all claims.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 501968.

Respectfully submitted,

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